Leukemia and subsequent solid tumors among patients with myeloproliferative neoplasms

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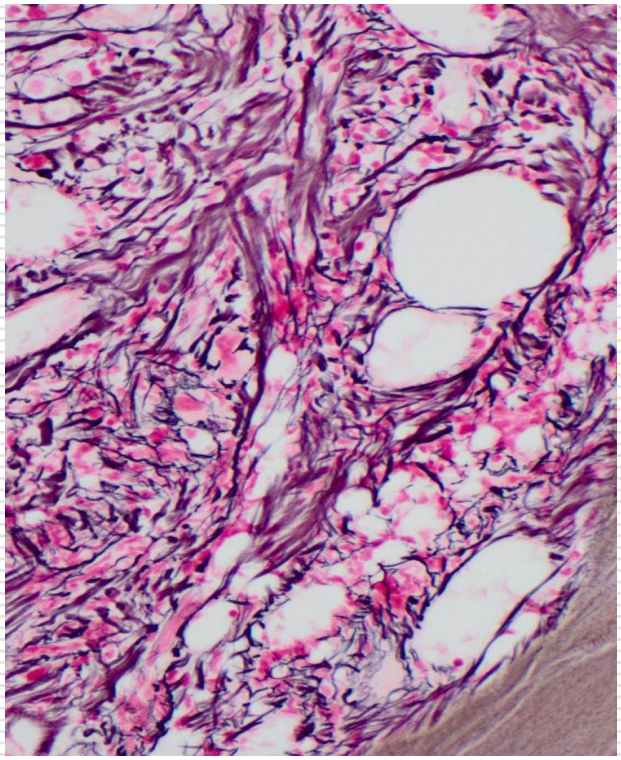
Leukemia and second tumors in MPN

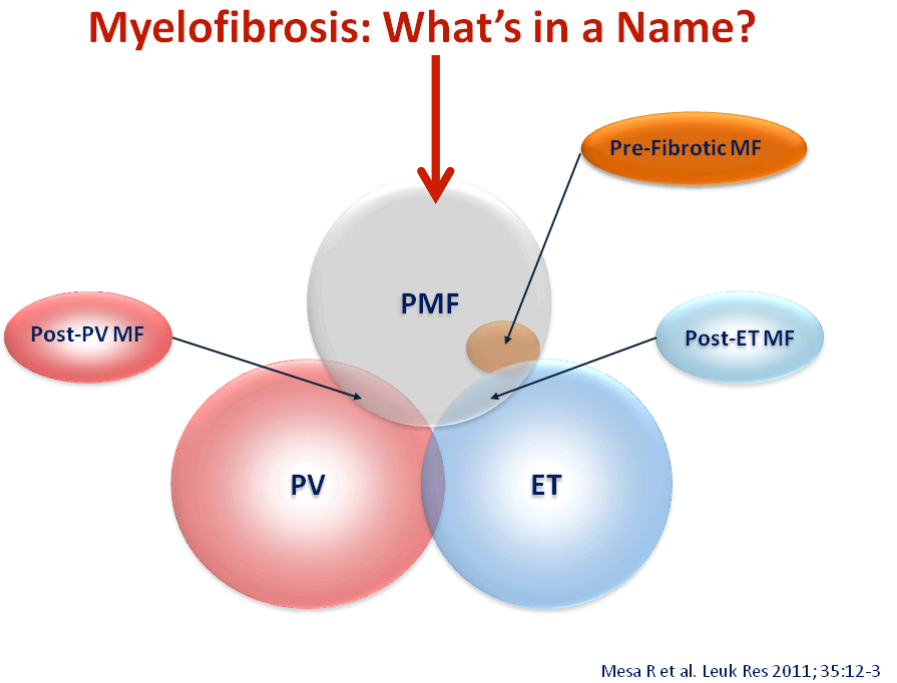
1. Epidemiology

- Registry
- Cohort studies

Myelofibrosis:

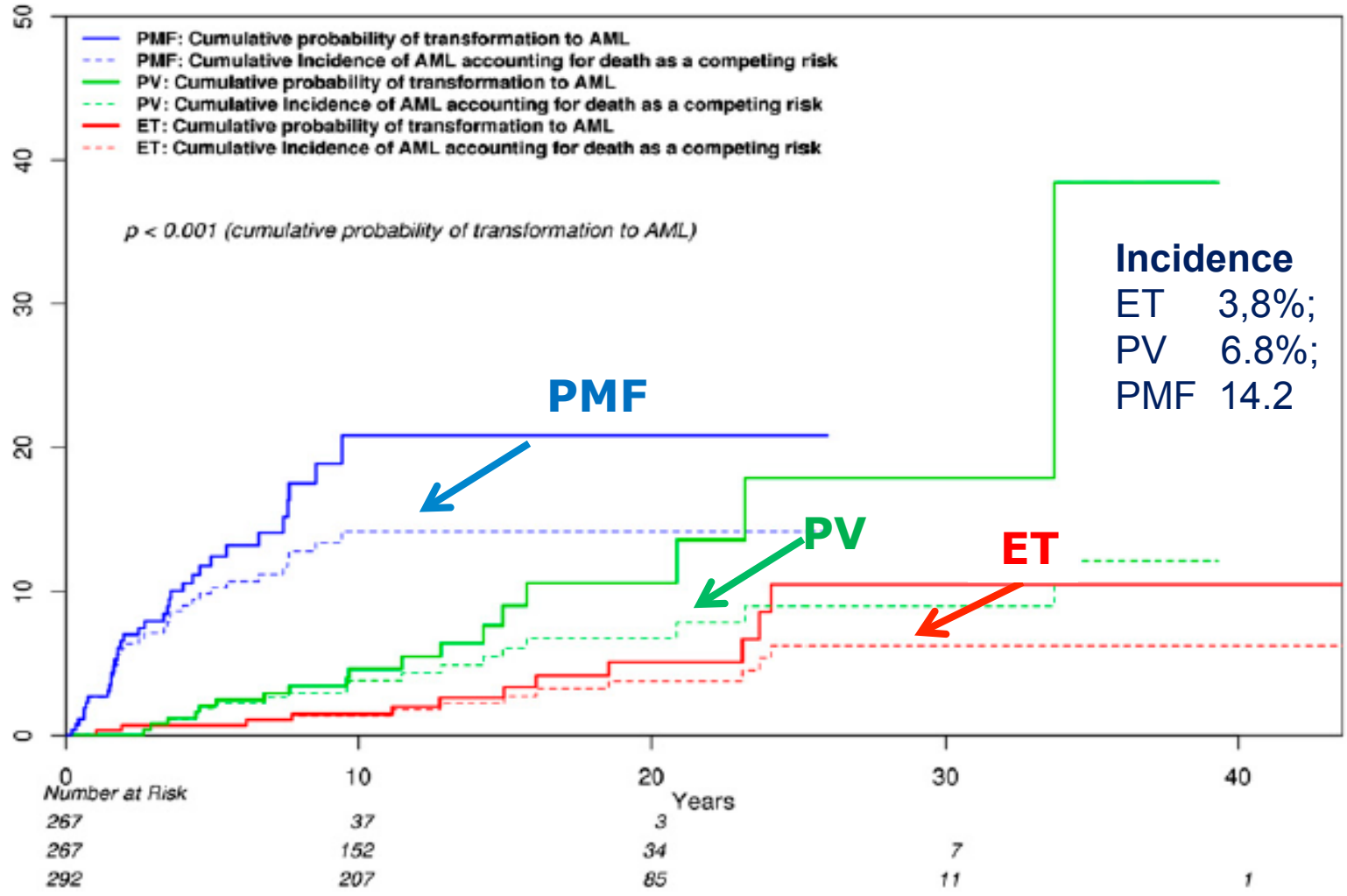
Heterogeneous disease including Primary MF, post ET/PV MF, early PMF





Mesa R et al. Leuk Res 2011; 35:12-3

Comparison of blastic transformation rates among 865 Mayo Clinic patients with MPN accounting for death as competing risk.



BLOOD, 16 OCTOBER 2014 • VOLUME 124, NUMBER 16

Cumulative incidence of myelofibrosis in PV/ET and acute leukemia: a literature review of incidence

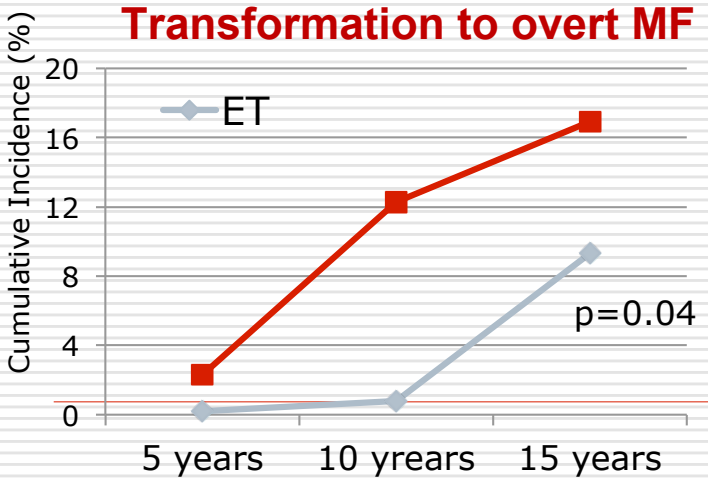
Diagnosis	at 10 years	at 15 years
Post-PV MF	4.9 – 6%	6 – 14%
Post-ET MF	0.8 – 4.9%	4 – 11%
Post-PV AML	**2.3 – 14.4%**	**5.5 – 18.7%**
Post-ET AML	**0.7 – 3%**	**2.1 – 5.3%**

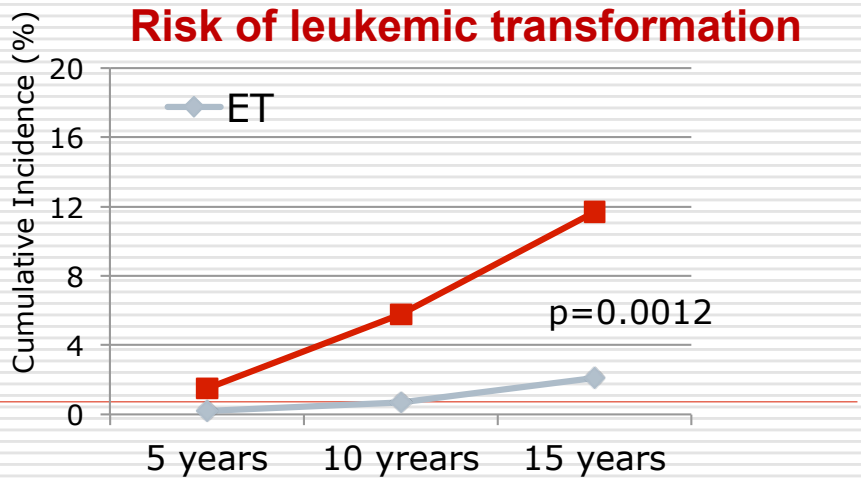
S Cerquozzi and A Tefferi, BCJ 2015

Disease progression in prePMF and ET according to WHO diagnosis

Event	No. of Events	% of Events	Incidence per 100 Patient-Years	IRR	*P*	5-Year Cumulative Incidence (%)	10-Year Cumulative Incidence (%)	15-Year Cumulative Incidence (%)
Thrombosis								
ET	109	12	1.7	1.1	.57	8.7	16.2	21.5
Early/prefibrotic PMF	26	15	1.9			6.6	17.9	25.4
Transformation to overt myelofibrosis								
ET	32	4	0.5	2.0	.04	0.2	0.8	9.3
Early/prefibrotic PMF	14	8	1			2.3	12.3	16.9
Leukemic transformation								
ET	8	1	0.1	5.2	.0012	0.2	0.7	2.1
Early/prefibrotic PMF	9	5	0.6			1.5	5.8	11.7
Death								
ET	87	10	1.3	2.1	.0002	3.0	14.8	24.6
Early/prefibrotic PMF	40	22	2.7			8.6	24.4	56.1

International Study on 1,104 Patients





Barbui et al., J Clin Oncol. 2011;29:3179-3184

Leukemia and second tumors in MPN

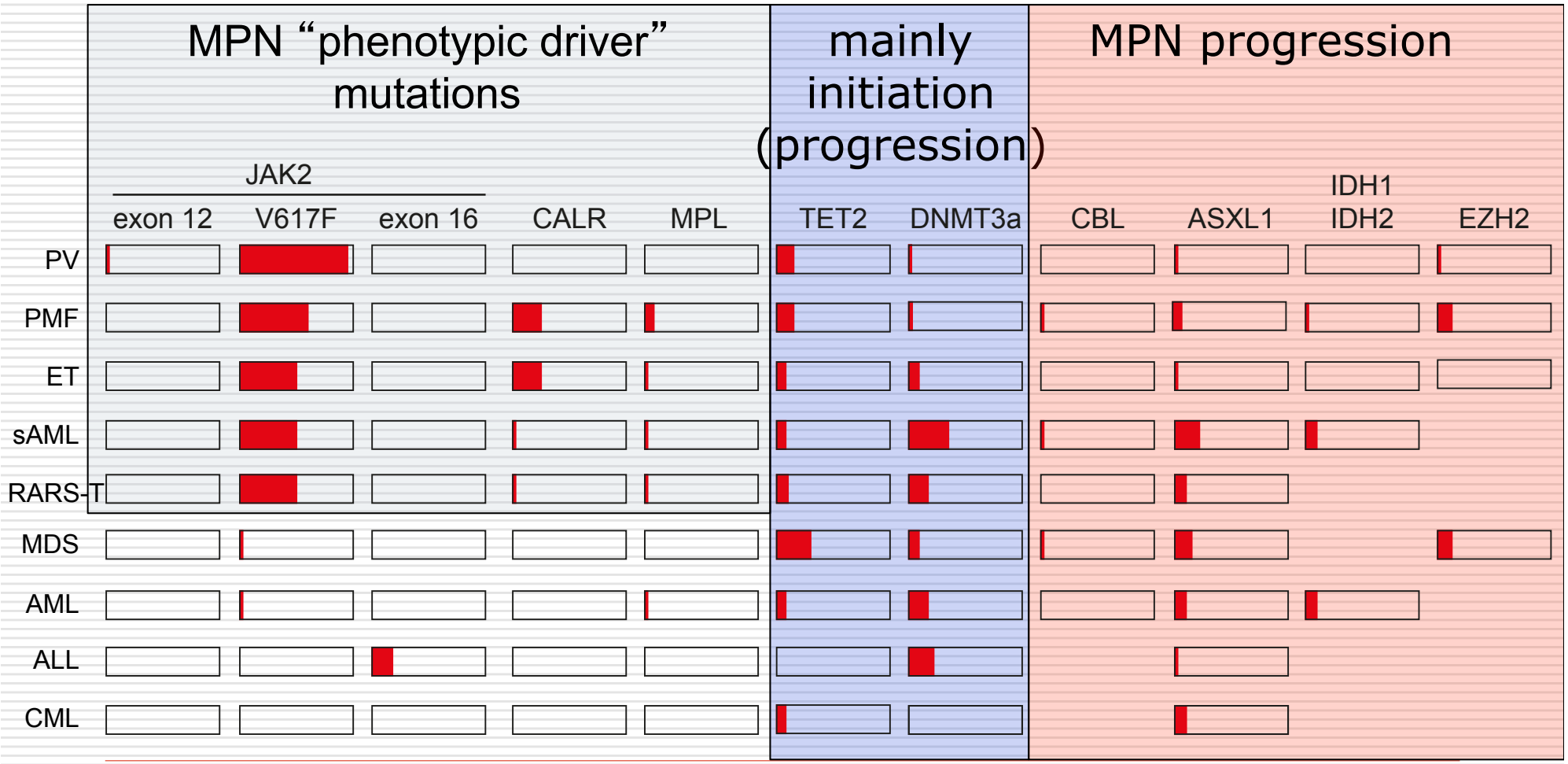
1. Epidemiology

- Registry
- Cohort studies

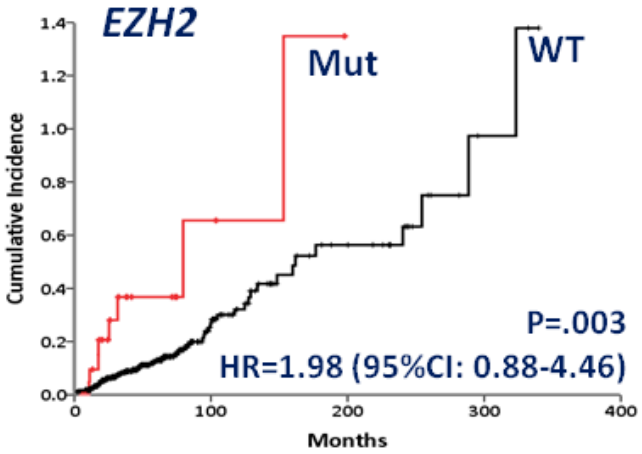
2. Risk factors

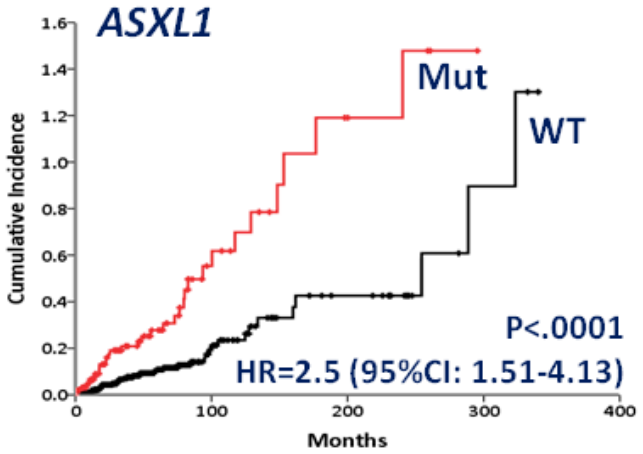
- Somatic mutations and cytogenetics
- Inflammation
- Stage of disease
- Cytoreductive drugs

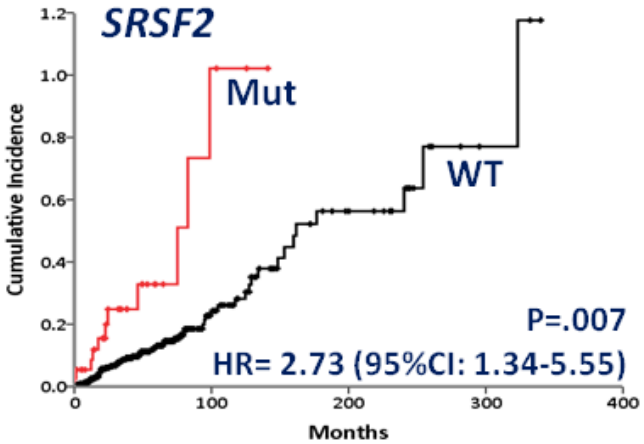
Somatic mutations in MPNs

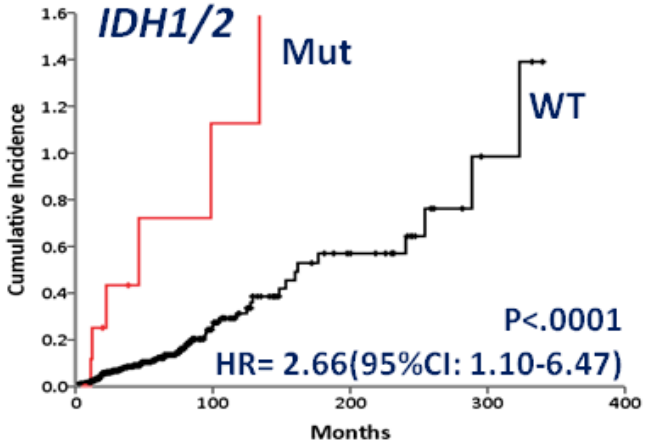


PMF: Mutations Associated with Blast Phase at Multivariate Analysis





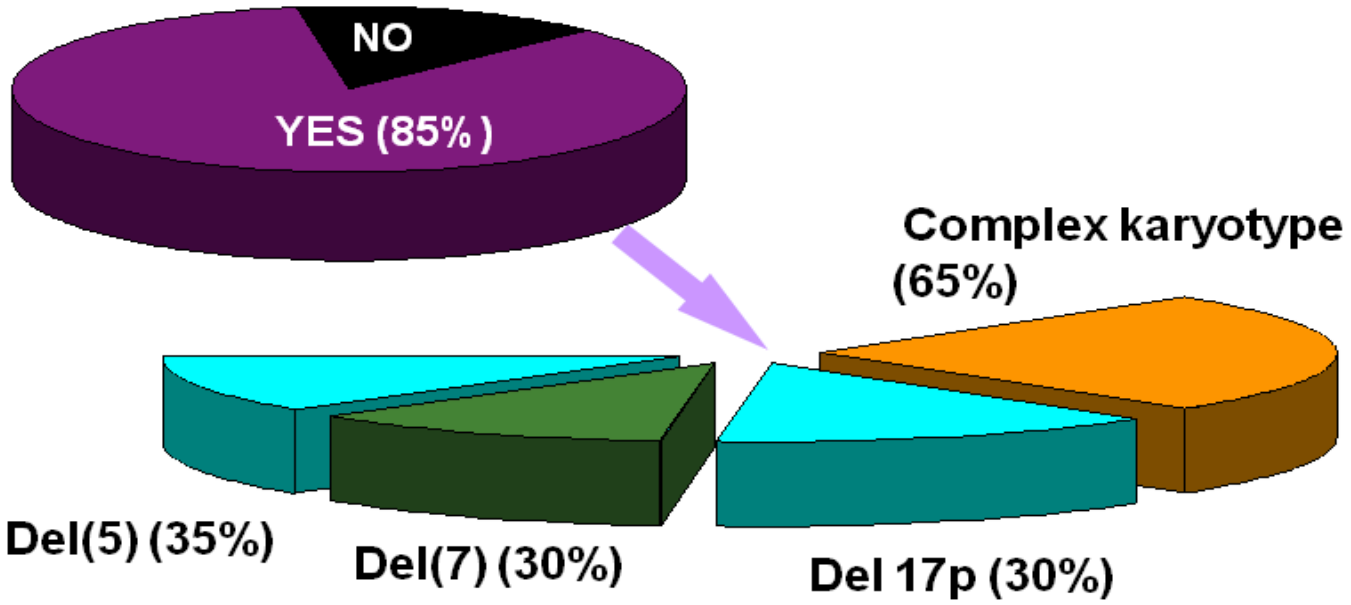




* Competitive Risk Analysis

Guglielmelli, P. *et al.*, ASH 2012; Abs. 431

Blast Phase MPN: Cytogenetic Abnormalities

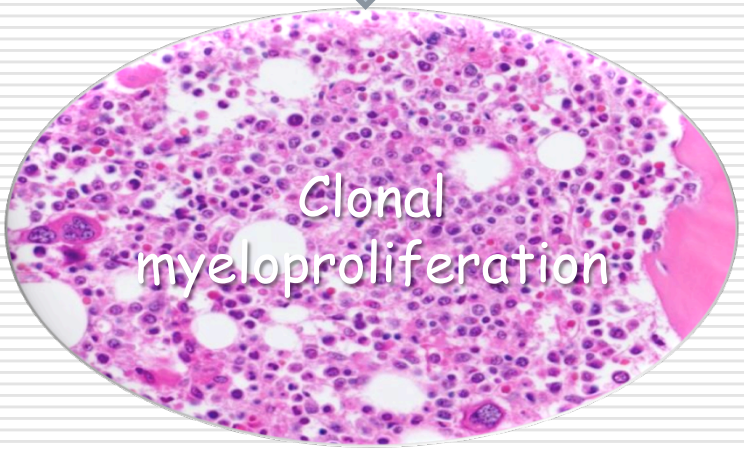


Role for inflammation as a driver and/or a consequence of clonal evolution in MPNs?

Clonal disorders in an inflammatory context

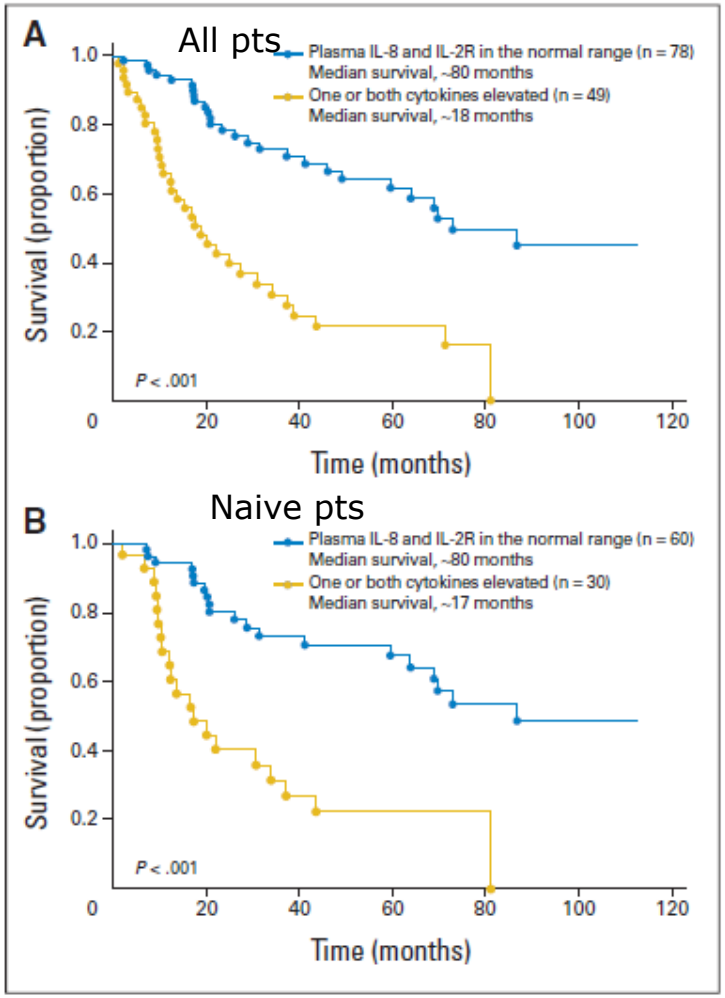
Bad seed
Jak2, MPL, CALR, TET2 mutations…

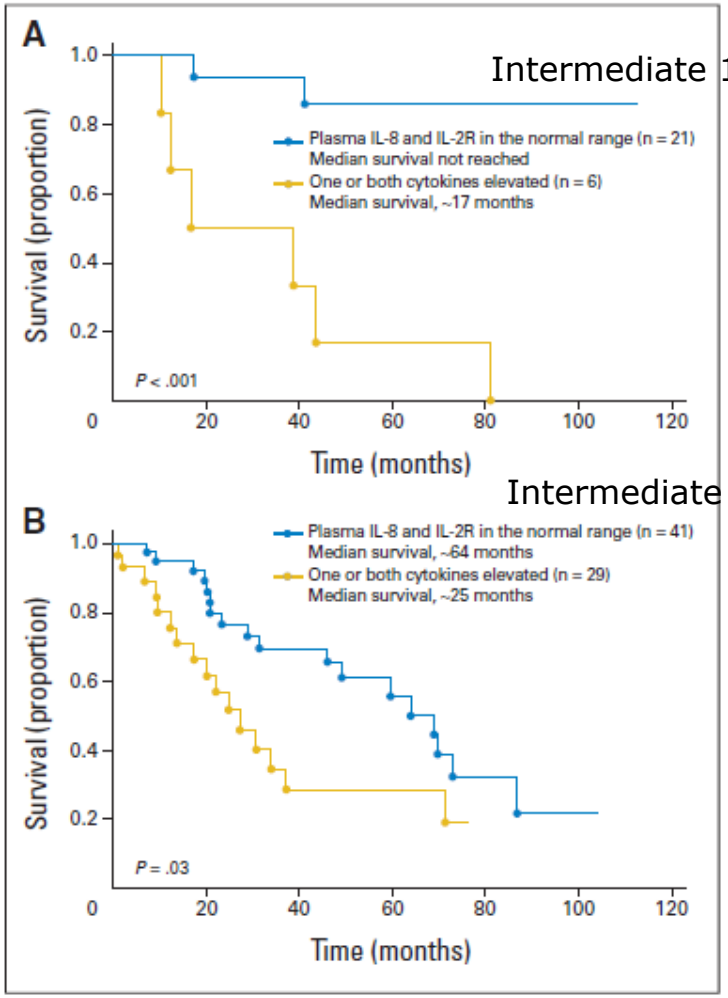
Bad soil
Persistent/chronic injuries ?



Chronic inflammation & BM stroma remodeling (Cytokine Storm, ECM, ROS…)

Changes in the levels of cytokines in Myelofibrosis distinguish two prognostic groups in intermediate-1 and 2.

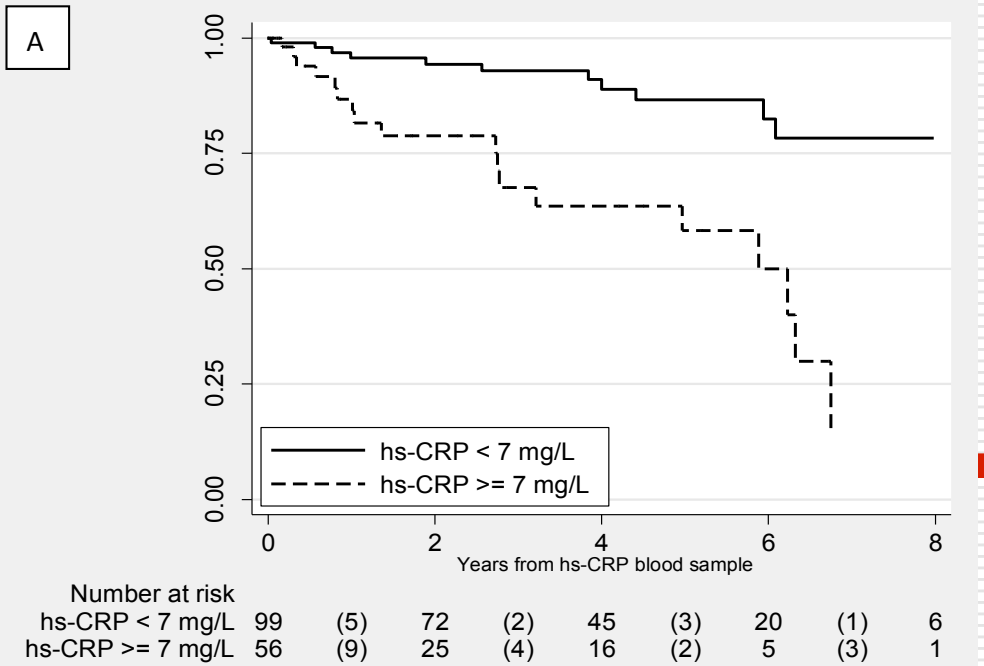


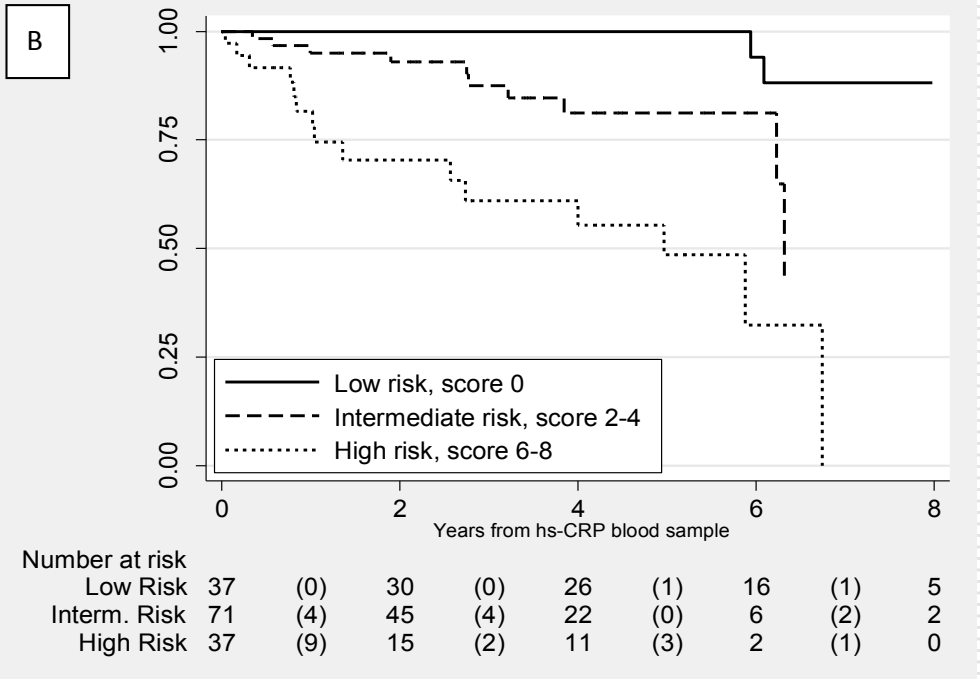


Tefferi et al. JCO 2011 .

CRP and Leukemia-free survival in PMF

by high (≥7mg/L) and low (<7mg/L) levels of hs-CRP (A) and according to the new scoring system (B).

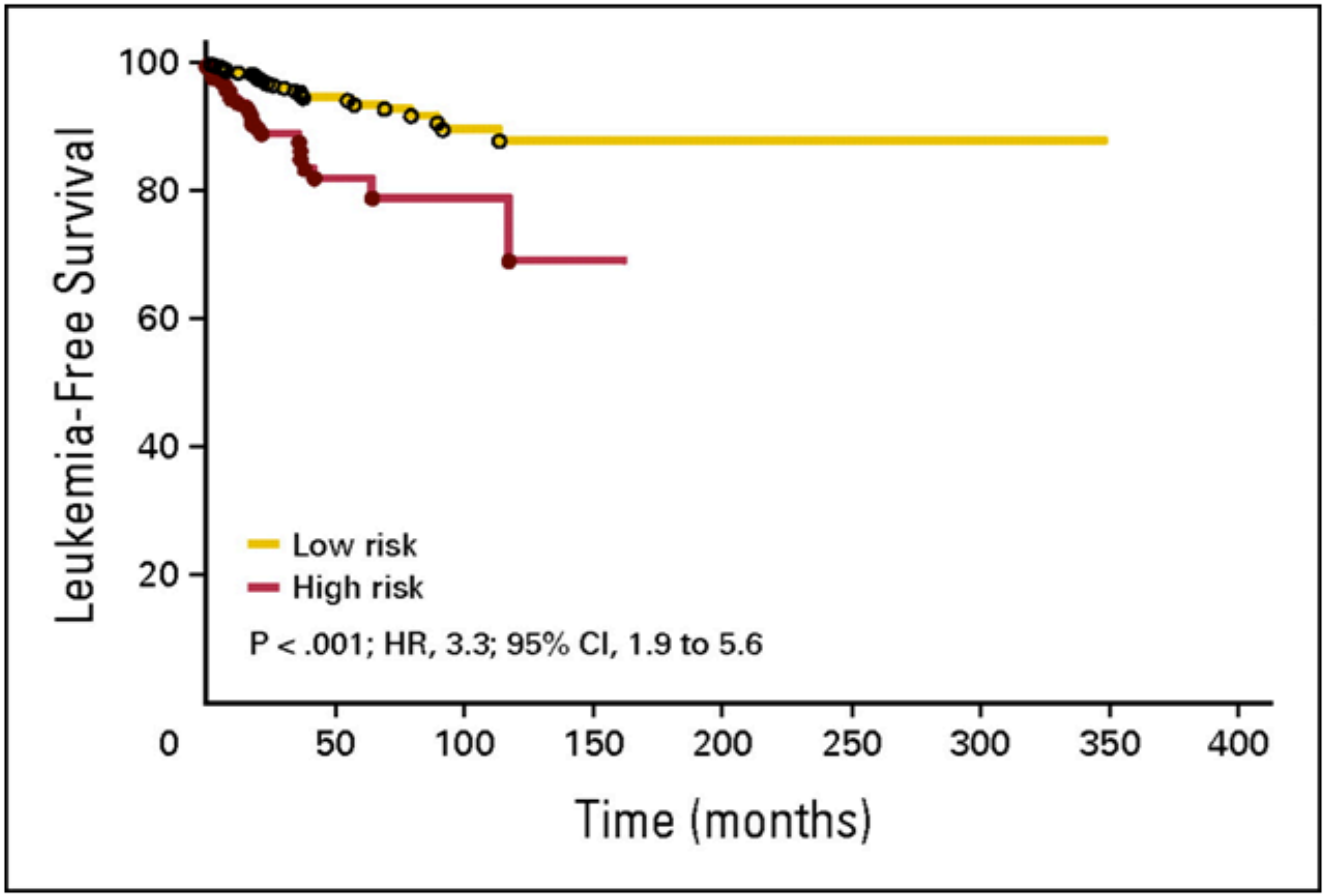




Barbui T, et al.
Elevated C-Reactive Protein is associated with shortened leukemia-free survival in patients with myelofibrosis
Leukemia (2013) 27, 2084–2086

Leukemia-free survival in PMF stratified by DIPSS-plus (n = 793)

Thrombocytopenia and unfavourable karyotype predicted for leukemic transformation



Gangat N et al., JCO 2011;29:392

Risk for AML/MDS transformation in PH-neg Chronic Myeloproliferative Neoplasms-

A population based nested case-control study

11,039 pts with MPN from the Swedish Cancer Registry
PV=138 ET=32 MF=21

193 AML and **13 MDS** (cases) compared with matched controls
Median time from diagnosis to AML/MDS was 7 years (0.5-35 yr)

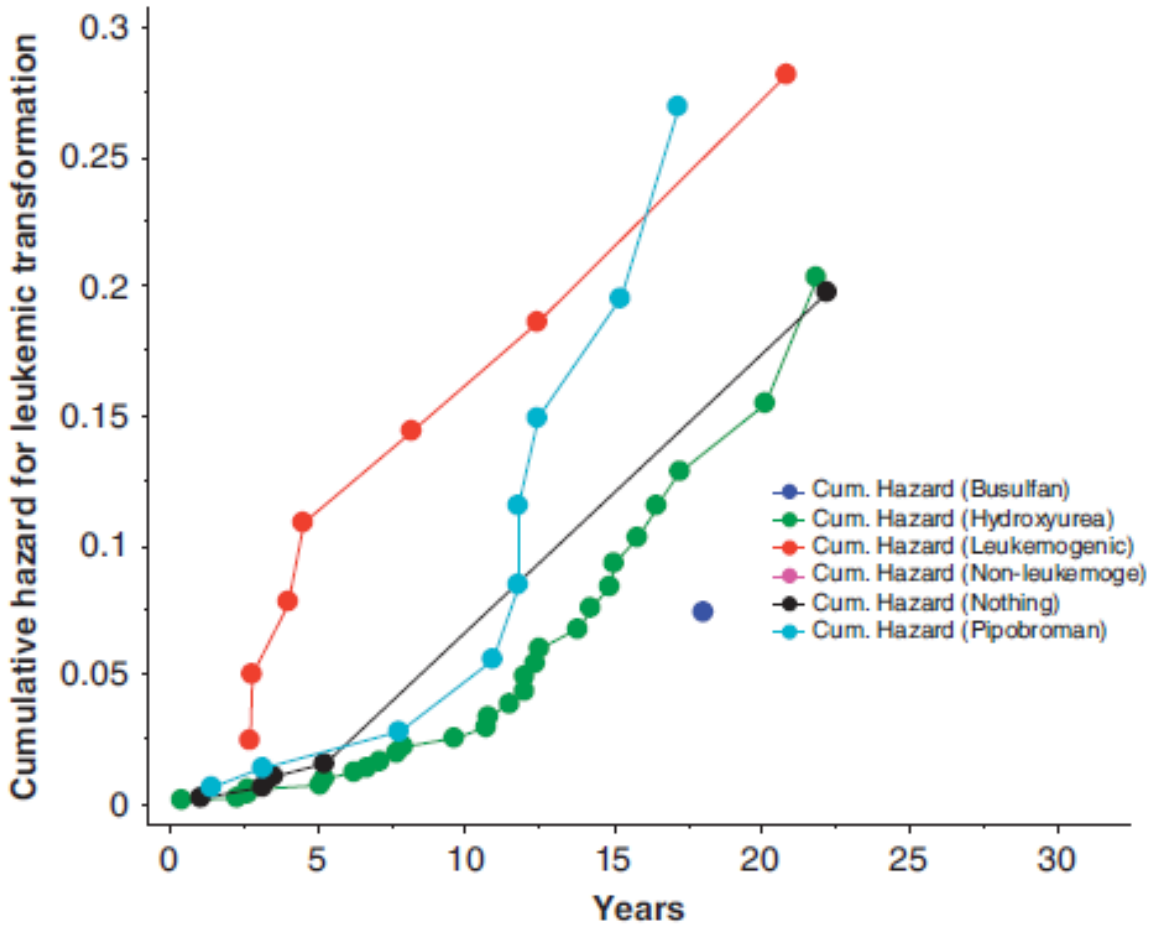
Exposure to Hydroxyurea (different dosage from <500g to>1000 g) compared to no exposure : Odd Ratio 1.07 (0.42-2.70)

25% of AML/MDS in untreated patients

Conclusion:HU did not significantly increase the Risk for transformation to AML/MDS

JCO 29,2410-2415, 2011

Cumulative incidence and time to event for AML transformation among 1545 pts stratified by the first cytoreductive drugs they were exposed to.



Leukemia (2013) 27, 1874–1881

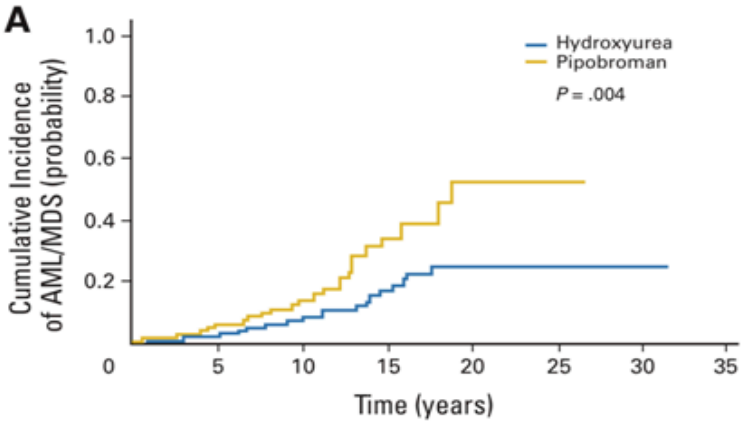
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Treatment of Polycythemia Vera With Hydroxyurea and Pipobroman: Final Results of a Randomized Trial Initiated in 1980

Jean-Jacques Kiladjian, Sylvie Chevret, Christine Dosquet, Christine Chomienne, and Jean-Didier Rain

- Evolution to AML/MDS

	10 years	15 years	20 years
Total cohort	9.8%	24%	34%
HU (ITT)	6.6%	16.5%	24%
Pipo (ITT)	13%	34%	52%



FIM FRENCH INTERGROUP MYELOPROLIFERATIVE DISORDERS

Interferon and malignancies in Polycythemia Vera. Case-control study from ECLAP

	Control N=120 N (%) IR x 100 pts/yrs	**Only INF N=40** N (%) IR x 100 pts/yrs
Death from any cause	6 (5.0) 2.0	2 (5.0) 1.8
Total thrombosis	8 (6.7) 2.8	6 (15.0) 5.8
Hematological transformation and cancer	**9 (7.5) 3.0**	**0 (0.0) 0.0**
Hematological transformation (acute leukemia + MDS)	2 (1.7) 0.6	0 (0.0) 0.0
Myelofibrosis	4 (3.3) 1.4	0 (0.0) 0.0
Solid tumors	4 (3.3) 1.4	0 (0.0) 0.0

Barbui et al, unpublished

Ruxolitinib in MF Adverse Events: 5-Year Final Study Results (exposure adjusted)

Preferred Term, n (exposure-adjusted rate)	Ruxolitinib Randomized (n = 146)	Ruxolitinib Randomized + Extension (n = 146)	BAT Randomized (n = 73)	Ruxolitinib Crossover (n = 45)	Total Ruxolitinib (n = 191)
Patient-year exposure	170.12	409.52	66.98	79.70	489.22
Bleeding events					
Bruising	24 (14.1)	38 (9.3)	6 (9.0)	12 (15.1)	50 (10.2)
GI bleeding	10 (5.9)	16 (3.9)	2 (3.0)	4 (5.0)	20 (4.1)
Intracranial	2 (1.2)	2 (0.5)	0	1 (1.3)	3 (0.6)
Other	42 (24.7)	60 (14.7)	14 (20.9)	18 (22.6)	78 (15.9)
Infections					
Herpes zoster	9 (5.3)	16 (3.9)	0	6 (7.5)	22 (4.5)
Pneumonia	8 (4.7)	21 (5.1)	7 (10.5)	4 (5.0)	25 (5.1)
Sepsis/septic shock	5 (2.9)	12 (2.9)	0	3 (3.8)	15 (3.1)
Tuberculosis	1 (0.6)	2 (0.5)	0	0	2 (0.4)
UTI	23 (13.5)	37 (9.0)	5 (7.5)	10 (12.5)	47 (9.6)
Tumors					
Malignancies	12 (7.1)	31 (7.6)	3 (4.5)	4 (5.0)	35 (7.2)
NMSC	9 (5.3)	25 (6.1)	2 (3.0)	1 (1.3)	26 (5.3)

8 patients (5.5%) in the ruxolitinib arm and 5 patients (6.8%) in the BAT arm developed AML over the course of follow-up

AML, acute myeloid leukemia; GI, gastrointestinal; NMSC, nonmelanoma

Leukemia and second tumors in MPN

1. Epidemiology

- Registry
- Cohort studies

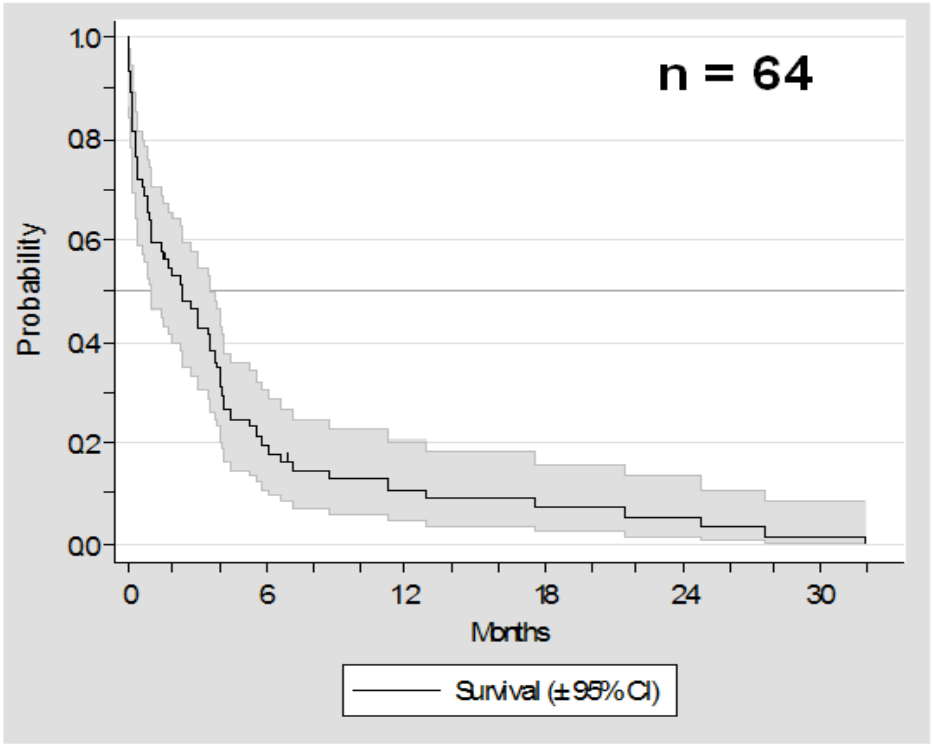
2. Risk factors

- Somatic mutations and cytogenetics
- Inflammation
- Stage of disease
- Cytoreductive drugs

3.Therapy

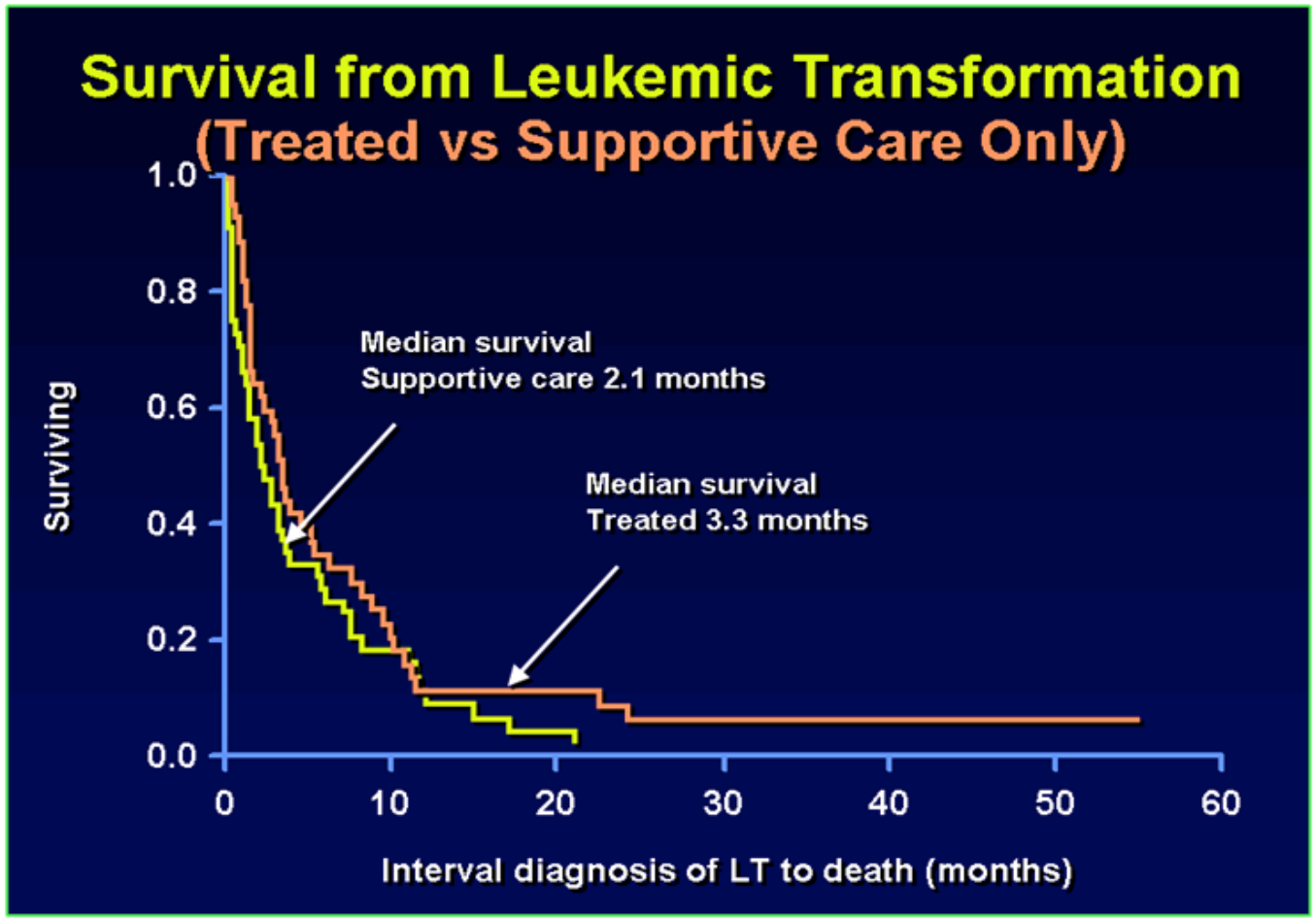
- Supportive
- AML-like treatment
- Stem cell transplantation
- JAK2 inhibitors

Survival after Leukemic Transformation in ET and PV



Hernandez-Boluda et al., *Blood* 2012; 119: 5221-5228

Survival after Diagnosis of Blast Phase MPN (N= 91; BP post-MF)



Mesa et al., *Blood* 2005; 105:973-977

Allo-SCT in Blast Phase MPN

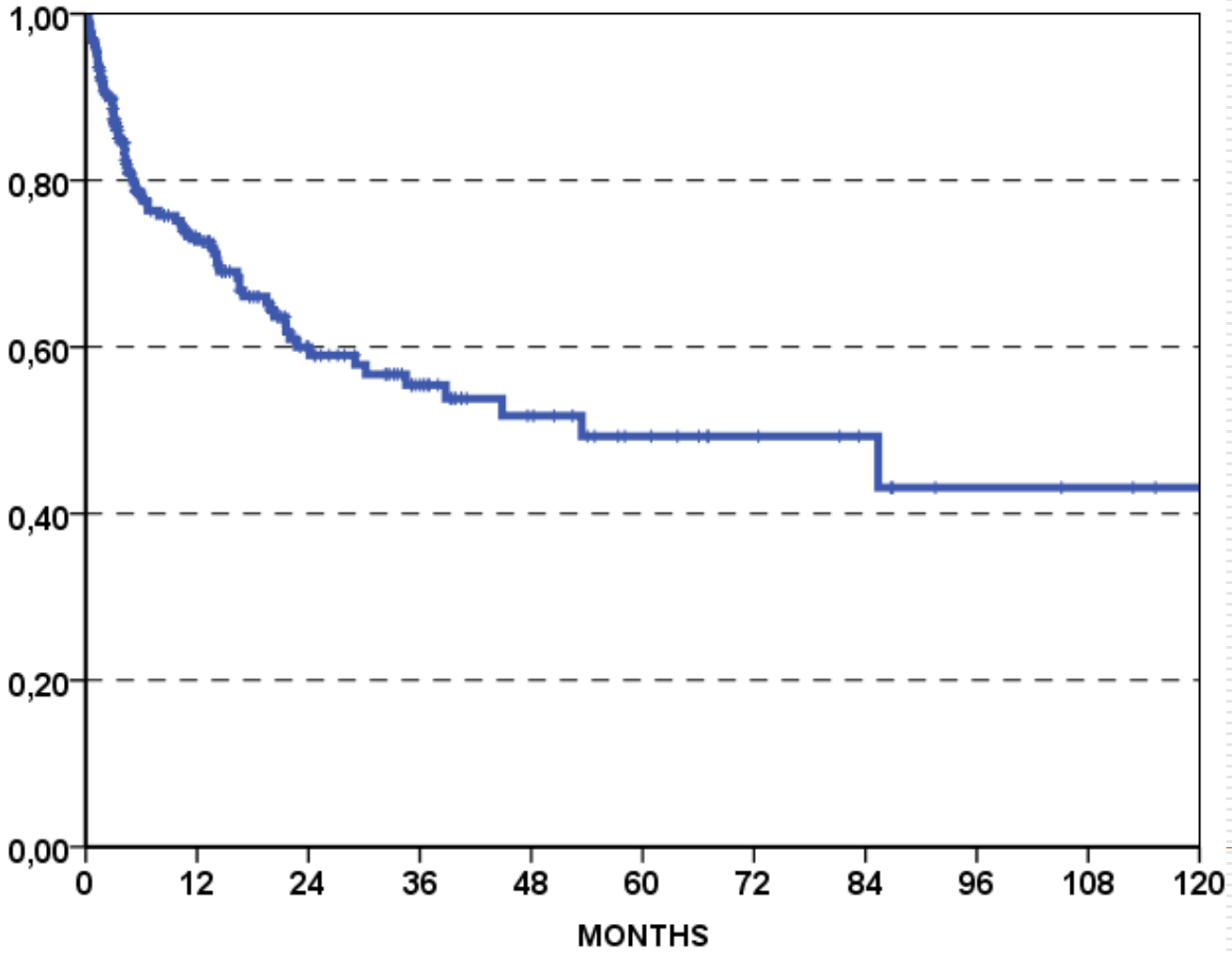
	MD Anderson	Mayo Clinic
No. of patients	14	8
Median age (range)	59 (50-67)	54 (44-72)
Status at SCT	CR: 6	CR: 5
RIC regimen	9	6
TRM *	29%	0%
PFS *	49%	75% **

* At 2 years; ** all patients were in CR at SCT

Ciurea *et al.*, Biol Blood Marrow Transplant 2010;16:555
Cherington *et al.*, Leuk Res 2012; 36:1147

Allogeneic SCT in AML and post-PV/ET MF

EBMT database (n=250)



Overall survival
<55y: 65%
>55y: 47%

sAML: 28%
sMF: 62%

Related: 65%
Unrelated: 50%
Mismatch : 30%

Rambaldi et al. EBMT 2011

Investigational drugs (II)

New Drugs in BP-PMF

Drug	No. of pts.	Outcome
Ruxolitinib [1]	18	CR: 2; PR:1 (OR 17%)
Azacitidine [2]	26	CR: 2; PR:1 (OR 12%)

[1] Eghtedar *et al.*, Blood 2012; 119:4614-18
[2] Thepot *et* al., Blood 2010; 116:3735-42

CONCLUSION

- The MPNs have a tendency to evolve into a blast phase. And are associated with higher risk to develop second tumors
  This tendency can be exacerbated by the genetic profile
  and by the use of some drugs

- In PMF, the role of the *JAK2* mutation is controversial; mutations in the ASXL1,EZH2,IDH1/2 and SRSF2 genes are strong predictors of blast phase

- The prognosis is very poor. In candidates for allo-SCT, CR should be achieved by AML therapy; for the remainder palliative or experimental therapies are reasonable options.